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PRINCIPAL INVESTIGATOR: Heiddis Valdimarsdottir, Ph.D.

CONTRACTING ORGANIZATION: Sloan-Kettering Institute for Cancer Research
New York, New York 10021

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To-date 41 women have been recruited for the experimental study and initial data have been entered. As we have only nineteen women with family histories of breast cancer and 22 women without a family history of breast cancer it would be premature to compare these two groups of women. The preliminary results are therefore presented for the whole sample. The results indicate that acute stressors induce a biphasic response of Natural Killer Cell Activity (NKCA). The 15 minute stressor period in this study was followed by an acute increase in NKCA followed by a reduction below baseline levels 30 minutes later. This finding may help explain discrepancies between the reduced NKCA reported in naturalistic stress studies and the immediate increases in NKCA so far reported in short term experimental studies. These findings have methodological implications for human experimental studies suggesting that NKCA should be assessed at multiple time-points over a period of at least 45 minutes after stressor onset in order to capture the full stress-induced NKCA response. Once enough data has been collected we will be able to examine possible differences in stress responses between women with and without family histories of breast cancer.

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Introduction

Healthy women with family histories of breast cancer, who are at increased risk for developing the disease, have been reported to have reductions in immune function (reduced natural killer cell activity) compared to women without family histories of cancer in their families (Strayer, Carter & Brodsky, 1986). Consistent with theories of immune surveillance against neoplastic disease (Trinchieri, 1990), such reductions could contribute to the increased risk of breast cancer in women at familial risk for breast cancer. The reduced natural killer (NK) cell activity in women with family histories of breast cancer have previously been attributed solely to heritable deficits in immune function. However, the cumulative evidence that psychological factors (e.g., distress) can affect immune function (see review by Herbert & Cohen, 1993) suggests two ways in which psychoimmune mechanisms may contribute to the immune deficits in these women. First, as women at familial risk for breast cancer have been reported to be more distressed (see review by Lerman & Schwartz, 1993), distress induced immune suppression may contribute to their immune deficits. Second, women at familial risk for breast cancer may be psychobiologically more reactive and/or immunologically more sensitive to psychological challenges.

Two interrelated studies, one naturalistic and another experimental are being conducted to address these issues.

Body

The Naturalistic Study: This study seeks to examine the contribution of distress-induced immune alterations to the reduced NK cell activity in healthy women with family histories of breast cancer. Three major questions are being addressed: First, are healthy women, who are at familial risk for breast cancer, more psychologically distressed than women at normal risk (with no history of cancer in their families)? Second, do healthy women at increased familial risk for breast cancer also show evidence of reduced NK cell activity? Third, does increased emotional distress contribute to the reductions in NK cell activity associated with familial risk for breast cancer?

Procedure: Women with family histories of breast cancer in first degree relatives (Risk Group) and women without family histories of breast cancer in first or second degree relatives (Comparison Group) are being recruited. These women are assessed on three separate days approximately one month apart (controlling for possible effects of menstrual cycles), at the same time of day (controlling for circadian effects). One woman from each of the Groups are assessed concurrently. At each of these assessments subjects complete standardized questionnaires (see study measures section 4.6 in the grant application), and after at least 30 minutes of rest, blood samples are collected for immune and endocrine measures (see sections 4.8 and 4.9 in the grant application).

Results: Since last report we have recruited a total of 52 women with (N=29) and without (N=23) family histories of cancer. In accordance with our Statement of Work for year 2 (see grant application) data are being entered and verified. In addition, initial data analyses have been conducted and preliminary results (see Progress Report for Year 1) indicate that women with family histories of breast cancer: 1) have higher levels of cancer specific distress; 2) have higher levels of general distress; and, 3) perceive themselves to be at higher risk for developing breast cancer, compared to women without histories of cancer in their families. In addition, the results suggest that perceived risk of breast cancer contributes to the higher levels of general distress indirectly, by increasing cancer specific distress.

The Experimental Study: This study seeks to examine the possibility that increased psychophysiological reactivity and/or immunological sensitivity to psychological challenges could contribute to the reduced natural cytotoxic activity in healthy women with family histories of breast cancer. Three major questions are being addressed: First, do healthy women at increased familial risk for breast cancer also show increased psychological reactivity to experimental stressors (mental tasks)? Second, do healthy women with family histories of breast cancer evidence greater immunologic sensitivity to experimentally-induced distress? Third, is the increased immunological sensitivity to distress in healthy women at increased familial risk for breast cancer due to differences in sympathetic responses and/or cortisol responses to the experimental stressors?

Procedure: Women who have completed the Naturalistic study are recruited for the experimental study. On the experimental days, participants are exposed to two consecutive mental tasks that have been shown to affect psychophysiological reactivity (i.e., self-reported distress, cardiovascular changes, endocrine changes) as well as immune measures (i.e., NK cell activity, lymphocyte proliferation) (e.g., Manuck, Cohen, Rabin et al., 1991; Stone, Valdimarsdottir, Katkin et al., 1993). Psychological distress is assessed (Profile of Mood States and Visual analog Scale; see Section 4.6 in the grant application) and blood samples for immune and endocrine assessments (see Sections 4.8 an 4.9 respectively in the grant application) are collected after a resting period and during and after stressor exposure at 15 to 30 minute intervals. Cardiovascular activity is assessed throughout the session.

Results: Since last progress report 42 women have completed the experimental study. In accordance with our Statement of Work (see grant application) data are being entered and verified. In addition we have analyzed some of the data and results have been presented and accepted for presentation at scientific conferences (see Appendix A and B). Supporting one of our study hypotheses initial data analyses suggest that women with family histories of breast cancer are psychobiologically and immunologically more reactive to laboratory stressors than women without family histories of breast cancer (see Appendix A). In addition, initial data analyses indicate that acute stressors induce a biphasic response of NK cell activity (see Appendix B).

Conclusions

The Naturalistic Study: Preliminary results confirm previous reports that women with family histories of breast cancer have high levels of general and cancer-specific distress (see review by Lerman and Schwartz, 1994). Higher levels of perceived risk of breast cancer contributed to higher levels of general distress indirectly by increasing cancer specific distress. These findings raise the possibility that effective genetic counseling may substantially reduce both cancer-specific and general distress. The hypothesis that higher levels of general distress and/or cancer-specific distress affect immune function in women at familial risk for breast cancer will be examined upon completion of the data collection in year 3 of the study (see below).

In line with our Proposed Statement of Work (see grant application) we plan to recruit approximately 110 women during year 3 of the study, thus it is anticipated that approximately 260 women will have completed the Naturalistic Study by the end of year 3. In addition, data entry and verification will be completed which will allow us to address the major study hypotheses, and prepare and submit manuscripts for publications.

The Experimental Study: Preliminary results support the hypothesis that women at familial risk are psychobiologically and immunologically more reactive to psychological challenges than women without family histories of breast cancer. These results support the view that the chronic threat of cancer in individuals at familial risk is associated with increased psychobiological reactivity to acute stressors in their lives. The data thus suggest that the chronic distress associated with familial cancer risk may not only affect cancer surveillance behaviors, as previously reported, but may also have negative health consequences through changes in psychobiological reactivity.

In line with our proposed Statement of Work (see grant application), we will continue recruiting women into the experimental study, and expect to have a total of 64 subjects at the end of year 3 of the study. Data entry and data verification will continue and preliminary results will be submitted for presentations at scientific conferences and/or submitted for publication.

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Appendix A: Biphasic Changes in Natural Killer Cell Activity Following Acute Stress in Humans. Poster Presented at Research Perspectives in Psychoimmunology, April 1996

Appendix B: Familial Risk for Breast Cancer is Associated with Heightened Psychobiological Reactivity to Laboratory Stressors. Poster Accepted for Presentation at the Society for Behavioral Medicine 1997

Appendix C: Positive and Negative Mood: Association with Natural Killer Cell Activity. Manuscript Accepted for Publication

Appendix D: Psychosocial Factors and Secretory Immunoglobulin A. Manuscript Accepted for Publication

Appendix A

Biphasic Changes in Natural Killer Cell Activity Following Acute Stress in Humans

Poster Presented at Research Perspectives in Psychoimmunology, April 1996

A POSITIVE EMOTION THE EUSTRESS OF MIRTHFUL LAUGHTER MODULATES THE IMMUNE SYSTEM LYMPHOKINE INTERFERON-GAMMA.

Lee S Berk, and Stanley A. Tan, Schools of Medicine and Public Health, Loma Linda University Loma Linda, CA 92350 USA

Distress has been associated with immunosuppression partially modulated by increased neuroendocrine hormones such as epinephrine, corticotropin and cortisol. We have previously reported that a specific positive emotion, the eustress of mirthful laughter 1) decreases or attenuates neuroendocrine and stress related hormones (*Berk et al, Amer J Med Sci 298 390-6, 1989*). 2) increases spontaneous lymphocyte blastogenesis (*Berk et al Clin Res 36 435A,1988*). (3) increases NK cell activity (*Berk et al Clin Res 37 115A,1989*); and (4) increases activated T-cells, NK-cells, immunoglobulins (IgG, IgA, and IgM), and B-cells (*Berk et al Annals of Behav Med 15 S111,1993*). Interferon-gamma (IFN) is known to regulate proliferation, differentiation, and activity of T and B cells and ensures cooperation between T and B cells and NK cells in the adaptive immune response (*Michael et al J of Immuno 142 1095-1101,1989*). IFN is believed to be a major endogenous regulator of NK cell activity (*Solimonse et al Clin Immunol Immunopathol 24:1-7, 1982*). Since we have observed several immunological component changes during mirthful laughter, we suggest a possible relationship of either IFN production and/or modulation. Therefore, we further investigated this positive emotional eustress by studying 10 healthy fasting male subjects for changes of IFN peripheral plasma blood levels. All subjects volunteered and the study protocol was approved by the University IRB. The experimental group preselected and viewed a 60 min humor video Multiple blood samples were obtained through an iv catheter before (baseline), during (intervention), after (recovery) and the next day. Samples were assayed by an immunoenzymatic method for the quantitative measurement of IFN. Within group effects across time by repeated measures MANOVA showed a significant increase in the experimental subjects for IFN ($p=0.02$). Simple contrasts with baseline showed significant increases in IFN at intervention ($p<0.001$), during recovery ($p<0.001$), and the next day ($p<0.001$) Plasma volume, hematocrit and total serum protein showed no significant change over the time points studied In conclusion, although further research is needed to elucidate these effects on specific regulation and the composite immune response, these data suggest that the eustress of mirthful laughter may be capable of modifying components of the immune response by the increase production of IFN and its subsequent immunomodulation.

BIPHASIC CHANGES IN NATURAL KILLER CELL ACTIVITY FOLLOWING ACUTE STRESS IN HUMANS.

Dana H Bovbjerg, Sandra Zakowski, Heiddis B Valdimarsdottir, Jean Mamakos, Libing Chen, Zakera Gandhi & Geri Waldman. *Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, NY 10021*

Background: Experimental studies of the effects of stress on human immune function have consistently demonstrated increased natural killer cell activity (NKCA) within minutes after a stressor (e.g., mental arithmetic), while naturalistic studies of life stress have typically revealed reduced levels of NKCA. We examined the possibility that stress may elicit biphasic changes in blood levels of NKCA, with acute increases followed by reductions in NKCA.

Methods: Following a 30' rest period, healthy women (N=16) were exposed to two mental challenges (a speech task and mental arithmetic) over a 15' interval, after which they again rested quietly for 90'. Blood samples were collected from an indwelling IV line at six times: 0' (baseline), 15' (immediately after the stressors), 30', 45', 75' and 105' (postbaseline). NKCA was assessed with a whole blood assay (Effector: target cell ratios = 1:1, 2, 4, 8).

Results: The effectiveness of the experimental manipulation was confirmed by significant increases in both self-reported emotional distress and blood pressure. Consistent with stress-induced changes in NKCA, multivariate repeated measures analysis of variance revealed a main effect of Time ($F(5,11) = 7.64$, $p < .003$) across all E:T ratios. Consistent with the hypothesized biphasic changes in NKCA after stress, statistical contrasts to the baseline values revealed an increase ($p < .0001$) in NKCA immediately after the mental challenges (15' sample), followed by a decrease ($p < .001$) from baseline across the next two samples (30' and 45'), and then a return to baseline ($p = .55$) in the later samples (75'' and 105').

Conclusions: The effects of stress on NKCA in humans may be more complex than previously appreciated. Although the mechanisms have yet to be determined, it would appear that acute mobilization of NKCA is followed by a period of reduced NKCA. Experimental models of stress-induced effects on immune function may have more heuristic value and generalizability if multiple points of assessment are included in future studies.

IMMUNOLOGICAL CHANGES ASSOCIATED WITH MARITAL INTERACTION IN BREAST CANCER PATIENTS AND THEIR SPOUSES

Catherine Classen[1], Sandra E. Sephton[1], Julia Zarcone[1], Karyn Angell[1], Helena C. Kraemer[1], Robert Carlson[2], Daniel Stites[3], & David Spiegel[1].

[1]*Department of Psychiatry and Behavioral Sciences and* [2]*Department of Oncology, Stanford University School of Medicine, Stanford, CA 94305-5544;* [3]*Department of Laboratory Medicine, University of California San Francisco School of Medicine, San Francisco, CA 94143-0134, U.S.A.*

The effect of stressful marital interaction on natural killer (NK) cell numbers and activity was examined in metastatic breast cancer patients and their spouses. Subjects were recruited for a prospective study of the effects of psychotherapy on cancer survival. Seventeen couples completed a 45-minute interactive task in which they discussed problems that have emerged because of the patient's cancer. The Profile of Mood States (POMS) was administered before and after the task, and the interaction was videotaped. NK cells were measured by flow cytometry and their function tested by the chromium-release method in serial blood samples drawn prior to the task, immediately post-task, and 24 hours post-task. POMS scores indicated that patients experienced increased mood disturbance during the session, but spouses did not. Repeated measures analyses demonstrated that the patients' physiological response to the intervention was different than that of their spouses. Patients demonstrated a significant decrease in NK cell function immediately post-task which failed to return to baseline levels by 24 hours after the task. Spousal NK cell function, however, was not significantly affected immediately post-task, and remained unchanged 24 hours later. The numbers and percentages of circulating NK cells decreased slightly, but changes did not reach significance in either group. The results indicate an immune function alteration in metastatic breast cancer patients which may reflect compromised ability of the system to adapt after marital stress. Alternatively, this type of marital interaction may simply elicit greater psychological stress in patients than in their spouses. Further studies will examine the possible role of marital stress on the rate of cancer progression, and the potential role of group therapy in moderating this effect.

Supported by grant 2R001 1 MH/CA47226-06 from NIMH and NCI.

EMOTION AND IMMUNE PROCESSES DURING MARITAL CONFLICT

Joel M. Dopp, Gregory E. Miller, Hector F. Myers, Suzanne Y. Felten, & John L. Fahey
University of California, Los Angeles
& University of Rochester, USA

Emotion has occupied a central role in models describing the impact of stress on the immune system. Several theories maintain that stressful events trigger negative emotional states, which subsequently alter immune processes through their effects on the autonomic nervous system and the neuroendocrine system. However, empirical evidence linking emotions to alterations in sympathetic, neuroendocrine and immune processes is limited. The goal of this study, therefore, is to investigate how affective responses during a naturalistic stressor relate to activation of the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system. We chose a marital-conflict resolution task as our naturalistic stressor because this task is highly personal, elicits a broad range of emotions, and closely resembles one type of stress that adults encounter regularly in their daily lives. Married couples participate in a 15-min conflict resolution task which is coded by trained observers who rate the extent to which subjects experience a number of discrete emotions (e.g., anger, sadness, anxiety). Blood pressure and heart rate are assessed before, during, and after the interactions. Peripheral blood is drawn at the same time points and used to quantify (a) circulating concentrations of cortisol and catecholamines; (b) circulating numbers of NK cells ($CD3^-/CD16^+/CD56^+$), cytotoxic/suppressor T cells ($CD3^+/CD8^+$), helper/inducer T cells ($CD3^+/CD4^+$), and granulocytes; (c) expression of cellular adhesion molecules (L-selectin [CD62L] and the hylauronic acid receptor [CD44]) which are thought to mediate leukocyte mobilization and activation; and (d) natural killer cell cytotoxicity. Preliminary data indicate that spouses who express high proportions of anger and fear during the marital conflict task show concomitant increases in blood pressure, heart rate, circulating numbers of natural killer cells, and natural killer cell cytotoxicity. Our conference presentation will include analyses of catecholamines, cortisol, and the above-mentioned cardiovascular and immune parameters on data from a minimum of 50 spouses.

Appendix B

Familial Risk for Breast Cancer is Associated with Heightened Psychobiological Reactivity to Laboratory Stressors

Poster Accepted for Presentation at the Society for Behavioral Medicine 1997

FAMILIAL RISK FOR BREAST CANCER IS ASSOCIATED WITH HEIGHTENED PSYCHOBIOLOGICAL REACTIVITY TO LABORATORY STRESSORS

Heiddis B. Valdimarsdottir[1], Dana H. Bovbjerg[1,2], Sandra G. Zakowski[1] Jean Mamakos[2] Julie Fasano[1] , Libing Chen[1] and Zakera Gandhi[1] . Memorial Sloan-Kettering Cancer Center and [2]Cornell University Medical College, New York, New York, 10021

Family history is the strongest predictor that a woman will develop breast cancer. This chronic health threat has been reported to elicit considerable distress. The present study is the first to test the hypothesis that women at familial risk for cancer also show increased immunologic reactivity to experimental stressors.

After a 30 minute baseline period, 14 healthy women (aged 25-50) at familial risk for breast cancer (Risk Group) and 28 women at normal risk (Comparison Group) were exposed to two classic laboratory stressors (a speech task and mental arithmetic) over a 15 minute interval. Natural killer cell activity (NKCA) was assessed with a whole blood assay before and after the stressors. Negative moods (visual analog scales) and cardiovascular activity were also assessed throughout the session.

Compared to baseline measures there were significant increases in NKCA, negative mood and cardiovascular activity following exposure to the stressors (p's $\leq .05$). Supporting the study hypothesis, these effects were more pronounced in the Risk Group. These women had larger increases in: NKCA (p's $\leq .04$), heart rate ($p \leq .01$), systolic blood pressure ($p \leq .02$), and negative moods ($p \leq .05$). These differences could not be accounted for by variability in baseline measures or demographic variables. Potential neuroendocrine mechanisms for these effects are under investigation.

These results support the view that the chronic threat of cancer in individuals at familial risk may be associated with increased psychobiological reactivity to acute stressors in their lives. The data thus suggest that the chronic distress associated with familial cancer risk may not only affect cancer surveillance behaviors, as previously reported, but may also have negative health consequences through changes in psychobiological reactivity.

Appendix C

Positive and Negative Mood: Association with Natural Killer Cell Activity

Manuscript Accepted for Publication

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POSITIVE AND NEGATIVE MOOD: ASSOCIATION WITH NATURAL KILLER CELL ACTIVITY

HEIDDIS B. VALDIMARSDOTTIR and DANA H. BOVBJERG

Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York NY, 10021

(Received 13 November, 1995; in final form 12 December 1995)

Negative mood (e.g., emotional distress) is known to affect immune function, but little research has addressed effects of positive mood. In the present study, positive and negative mood (over a day) were examined for their relations to natural killer cell activity (NKCA) in 48 healthy women. Results indicated that women reporting some negative mood (N = 26) had lower levels of NKCA than women who had no negative mood, while those with higher levels of positive mood had higher NKCA. However, as indicated by the significant interaction between positive and negative mood, the relation between positive mood and NKCA depended upon the women's experience of negative mood. Higher levels of positive mood were related to higher levels of NKCA only among the women who reported having some negative mood over the day. These results raise the possibility that positive mood may moderate, or buffer, the effects of negative mood on immune function.

KEY WORDS: Psychoneuroimmunology, positive mood, negative mood, natural killer cell activity.

INTRODUCTION

Individuals undergoing stressful life events have been found to have a higher incidence of a variety of illnesses that suggest immune system involvement (Brown and Harris, 1989; Holmes and David, 1989). As recently confirmed in a meta-analytic review (Herbert and Cohen, 1993) studies have consistently found altered immune function in individuals encountering various distressing life events including: loss of a spouse or loved one, divorce or marital separation, unemployment, taking care of a sick relative, and taking academic examinations. There is also evidence that undesirable day-to-day events (e.g., argument with spouse) can affect immune function (Stone, Neale, Cox, Napoli, Valdimarsdottir, and Kennedy-Moore, 1994; Stone, Marco, Cruise, Cox, and Neale, 1995). The possible effects of positive life events on immune function have received less research attention, but initial evidence suggests an association. For example, Stone and colleagues (1994) found that individuals reporting more desirable daily events (e.g., close interaction with spouse) had stronger salivary antibody responses (sIgA) to oral challenges with a novel antigen.

It has been hypothesized that the relations between life events (positive or negative) and alterations in immune function are mediated by changes in affective states which, in turn, lead to changes in neuroendocrine pathways and/or in health related behaviors

Correspondence to: Dr. Heiddis B. Valdimarsdottir, Department of Psychiatry, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York, 10021 USA, Tel: (212) 639-3279, E-mail: Heiddis@.neuro.MSKCC.org.

(Cohen, Kessler, and Gordon, 1995). Supporting the hypothesized role of negative affective states, Stone and colleagues (1995) reported that increases in negative mood mediated the relation between undesirable daily events and lower antibody responses to an oral antigenic challenge. Several other studies have shown that negative affective states are associated with alterations in various immune parameters, including: reductions in natural killer cell activity (Irwin, Daniels, Bloom, Smith, and Weiner, 1987; Bovbjerg and Valdimarsdottir, 1993); reduced lymphocyte proliferative responses (Linn, Linn, and Jensen, 1981); lower serum antibody responses to Hepatitis B vaccine (Jabaaij, Grosheide, Heijtink, Duivenvoorden, Ballieux, and Vingerhoets, 1993); and reduced salivary antibody responses to oral challenges with a novel antigen (Stone, Cox, Valdimarsdottir, Jandorf and Neale, 1987).

On the other hand, relatively little research has addressed the possible influence of positive affective states on immune function. Stone and colleagues have reported that increases in positive mood mediated the relation between desirable daily events and salivary antibody responses to antigenic challenge (Stone *et al.*, 1995). Relations between higher levels of positive mood and higher salivary antibody responses to antigenic challenges were also reported in two previous studies by this group (Stone *et al.*, 1987; 1994).

These studies on salivary antibody responses to oral antigenic challenges raise the possibility that positive and negative mood may have differential effects on immune function. However, it is not clear if immune measures besides salivary antibody responses are similarly affected. The present study focused on the possibility that NKCA may be differentially affected by positive and negative mood. Considerable evidence indicates that NKCA is particularly sensitive to emotional distress (O'Leary, 1990) but little research attention has been paid to the possible effects of positive mood on NKCA.

Consistent with previous naturalistic studies, we hypothesized that negative mood would be associated with lower levels of NKCA, while positive mood might prove to be associated with higher levels of NKCA. We also explored the possibility that positive mood might reduce the effects of negative mood on NKCA, as some researchers have suggested that positive emotions may serve as a stress buffer (Edwards and Cooper, 1988).

METHOD

Subjects

Women were recruited by announcements posted in staff areas of three contiguous medical centers. Participants (N = 48) reported having no chronic medical condition, no current use of medication and no symptoms of infectious disease in the last three days. The mean age was 38.8 years (range 22–63). The majority of the women were white (71%), single (71%), employed (85%), well educated (72% had attended college), and premenopausal (81%).

Procedure

Subjects were scheduled to come to the laboratory at the same time of day on two consecutive days. On the first day, basic demographic data were collected and subjects completed psychobehavioral questionnaires (see below). Blood was then collected for

assessment of NKCA (see below), conducted by a technician blind to the results of the questionnaires. On the second day of assessment, subjects again completed the psychobehavioral questionnaires and blood samples were collected.

Assessments

Demographic information was collected on a standard questionnaire to obtain information on age, race/ethnicity, and marital status (Bovbjerg and Valdimarsdottir, 1993).

Positive and negative affect was assessed, on both assessment days, using a questionnaire developed by Guadagnoli and Mor (1989). This questionnaire has 2 scales, positive and negative affect, which were derived from principal component analyses ofthe 65 mood adjectives in the Profile of Mood States (McNair, Lorr, and Droppleman, 1971). The two scales (positive and negative affect) each consist of 7 adjectives scored from 0 (not at all) to 4 (extremely), with results reported as the mean of all 7 items. In two independent samples of subjects, these investigators found that the scales for positive and negative mood had high alpha coefficients (> .70) and were independent of each other. We confirmed these high alpha coefficients (> .90) within each scale in the present sample, but found that the scales were inversely correlated ($r = -.49$, $p < .01$). Because of the high test-retest correlations across the two assessment days (p's < .01), the mean of each scale for the two days was computed and used in all subsequent analyses. It should be noted that during the course of the study the timeframe of the questionnaire was modified from "this week including today" (N = 20) to "today" (N = 28), reflecting considerations relevant to our ongoing research program. To ensure that this modification did not influence the results presented here, we entered this grouping variable as a covariate into the analyses described below; including this covariate did not alter any of the results.

Daily Habits (e.g., alcohol consumption) that may be influenced by affective states, and which could in turn influence immune function (Kiecolt-Glaser and Glaser, 1988), were assessed with a standard questionnaire (Bovbjerg and Valdimarsdottir, 1993). This questionnaire uses a self report format to assess: sleep, eating patterns, cigarette smoking, alcohol consumption, use of licit and illicit drugs, as well as infectious disease symptomatology, over the three days prior to the blood collection.

Complete blood counts (CBC) with differential were performed by a commercial laboratory (Methpath, Teterboro, NJ). Because of the high test-retest correlations across the two days of assessment (p's < .004) mean counts were computed and used in all subsequent analyses.

Natural Killer Cell Activity (NKCA) was assessed, on both assessment days, using peripheral blood mononuclear cells, isolated from heparinized blood samples by standard Ficoll-Hypaque gradient centrifugation (Bovbjerg and Valdimarsdottir, 1993). Cytotoxic activity against the classic NK-sensitive K562 tumor cell line was assessed in a standard ^{51}Cr release assay at three different effector to target cell ratios (10:1, 30:1 and 100:1), as previously described (Bovbjerg and Redd, 1992). Data from all effector to target cell ratios were included in the statistical analyses, as a more conservative approach than use of summary values such as mean cytotoxic activity or lytic units (Pollock Zimmerman and Fuchshuber, 1990). Because of the high test-retest correlations across the two days of assessment (p's < .01) the mean at each E:T cell ratio was computed and used in all subsequent analyses. It should be noted that repeated measures

ANOVA revealed no significant (p's > .25) differences (main effect of Time or interactions with Time) in NKCA between the two days of assessment.

RESULTS

Positive and negative mood

The mean level of negative mood in the study sample was 0.42 ± 0.90 (SD). Consistent with previous studies (Watson and Tellegen, 1985) the negative mood scores were highly skewed towards the low end (22 of the 48 subjects had negative mood scores of zero across the two days of assessment); in the subgroup of women with some negative mood the mean level of negative mood was 0.79 ± 1.10. The mean level of positive mood was 2.30 ± 0.85. Again consistent with previous studies (Watson and Tellegen, 1985), the positive mood scores were approximately normally distributed. Because of these different distributions, negative mood was treated as a dichotomous variable (women with some negative mood vs women with no negative mood) and positive mood was treated as a continuous variable in all subsequent analyses. The mean level of positive mood was 1.97 ± 0.65 in the subgroup of women with some negative mood, and 2.70 ± 0.91 in the subgroup of women with no negative mood.

Association between NKCA and affective states

The mean levels of NKCA in the study sample at the three effector to target cell ratios were: 19.5 ± 11.6 (10:1), 35.5 ± 15.7 (30:1), 53.1 ± 15.7 (100:1). The hypothesis that negative and positive mood would be differentially associated with NKCA was examined with multivariate regression analyses (using SAS General Linear Model), entering positive and negative mood as predictors. The possible role of positive mood as a stress buffer was examined by including the interaction term (positive X negative mood) in the analyses; including the interaction was all the more important because of the inverse correlation found between the mood scales (see Methods). The results indicated that positive mood was associated with higher levels of NKCA ($F(1,44) = 10.01$, $p = .002$) and negative mood was associated with lower levels of NKCA ($F(1,44) = 7.35$, $p = .009$) mood. The interaction between positive mood and negative mood was also significant ($F(1,44) = 8.05$, $p = .007$) across the three effector to target cell ratios. No significant relations were seen with the complete blood count data (i.e., numbers of white cells, lymphocytes, monocytes, or polymorphonuclear cells).

To determine the source of the significant interaction for NKCA, we examined the relations between positive mood and NKCA within the subgroups of women who reported no negative mood across the two days of assessment (N = 22) and those reporting some negative mood (N = 26). We first examined the relations between positive mood and NKCA in the subgroup of women who reported no negative mood. Regression with repeated measures revealed no significant main effect of positive mood ($F(1,20)=.06$, $p=.80$) or interactions with effector to target cell ratios (p's > .2). Higher levels of positive mood were not associated with higher levels of NKCA in the subgroup of women who reported no negative mood, as is graphically represented (at the 100: 1 effector to target cell ratio) by the flat regression line in the Figure. A similar pattern of response was seen at the other two effector to target cell ratios (not shown).

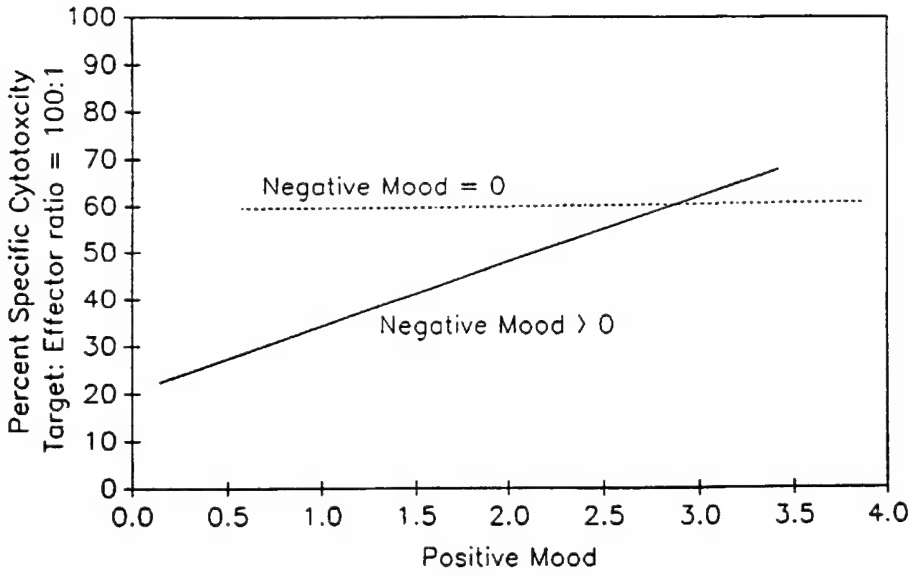

Figure 1 Relations between positive mood and natural killer cell activity in the subgroups of women who reported having some negative mood (solid line) and those who reported no negative mood over the two assessment days (dotted line)

On the other hand, there was a relation between positive mood and NKCA in the subgroup of women who reported some negative mood across the two days of assessment. Regression with repeated measures revealed a main effect of positive mood ($F(1,24) = 16.86$, $p < .001$), which accounted for 41% of the variance in NKCA; no significant interactions with effector to target cell ratios (p's > .2) were observed. Higher levels of positive mood were associated with higher levels of NKCA in the subgroup of women who reported no negative mood, as is graphically represented (at the 100:1 effector to target cell ratio) by the upward slop of the regression line in the Figure. A similar pattern of response was seen at the other two effector to target cell ratios (not shown).

Because there was variability in the intensity of negative mood within this subgroup of women reporting some negative mood over the assessment days, it was possible that variability in negative mood could have contributed to the relation between positive mood and NKCA. To examine this possibility, we entered negative mood as a covariate into the analysis described above; positive mood remained a significant predictor of NKCA across the three effector to target cell ratios ($F(1,23) = 15.92$, $p < .001$); again there were no significant interactions with effector to target cell ratio. We also considered the possibility that the subgroup of women who reported some negative mood may have had more variability in positive mood, which could provide an alternative explanation for why we only found a relation between positive mood and NKCA in the subset of women reporting some negative mood, but no such differences were found between the groups.

Do differences in demographic variables and/or daily habits account for the relations between NKCA and affective states?

To examine the possibility that individual differences in demographic variables or daily habits (e.g., amount of sleep) may have accounted for the results presented above, we examined the relations between these variables and NKCA in this sample, using repeated measures ANOVA for each variable (with effector to target cell ratio as a within-subject factor). The results revealed no significant main effects (p's $> .2$) on NKCA for any of the demographic variables, menopausal status, or daily habits and no significant interactions with target cell ratio.

DISCUSSION

The results of the present study revealed that women reporting some negative mood had lower levels of natural killer cell activity (NKCA) than women who had no negative mood over the two assessment days, while those with higher levels of positive mood had higher NKCA. However, as indicated by the significant interaction between positive and negative mood, the relation between positive mood and NKCA depended upon the women's experiences of negative mood. Higher levels of positive mood were related to higher levels of NKCA only among the women who reported having some negative mood over the days. Inspection of the Figure suggests that, within this subgroup of women, higher levels of positive mood are associated with higher levels of NKCA, which approach those of women who did not report any negative mood over the two days of assessment. These results raise the possibility that positive mood may moderate, or buffer, the effects of negative mood on immune function.

The possibility that positive emotions may serve as a stress buffer has been suggested by several investigators (Edwards and Cooper, 1988; Lazarus, 1991; Lazarus, Kanner, and Folkman, 1980). For example, Lazarus and colleagues (1980; 1991) have articulated three possible means by which positive emotions may serve as buffers. Positive emotions may: 1) enhance coping by providing a "breather" from ongoing stress; 2) help to sustain ongoing coping needed to resolve a challenge; or, 3) restore psychological resources depleted by stress. Empirical support for the stress buffering effects of positive mood is scant. Consistent with the hypothesis, Cohen and Hoberman (1983) have reported that the number of positive events experienced by an individual moderated the relation between negative life-events and depressive/physical symptomatology. Similarly, Reich and Zautra (1981) found that engaging in pleasant activities reduced distress only for individuals who also reported high levels of life stress.

To our knowledge, the present study is the first to consider the possible role of positive mood as a buffer, interacting with the effects of negative mood, on measures of immune function. Previous studies of affective states and immune function have focused on the direct effects of positive and negative mood. For example, Stone and colleagues (1987, 1984) found that negative mood was associated with smaller antibody responses to challenge antigen, while positive mood was associated with larger antibody responses. These studies, however, did not examine possible interactions, making comparisons to the results of present study problematic.

It is also difficult to compare the results of the present study to those of two recent studies in which positive and negative moods were experimentally induced (Knapp, Levy, Giorgh, Black, and Fox, 1992; Futterman, Kemeny, Shapiro, and Fahey, 1994).

Knapp and colleagues (1992) found no significant changes in NKCA following the induction of maximally disturbing or maximally pleasurable emotional experiences. Futterman and colleagues (1994) found transient increases in the levels of NKCA following the induction of either positive or negative mood states by "method" acting techniques. Neither of these studies was designed to examine the possible buffering effect of positive mood. It would be of interest in future studies to experimentally test the buffering effects of positive mood, perhaps following methods analogous to those of Gerin and colleagues, who have recently experimentally demonstrated the buffering effects of social support on cardiovascular reactivity (Gerin, Milner, Chawla, and Pickering, 1995).

The results ofthe present naturalistic study should be interpreted cautiously for several reasons. First, the study sample was relatively modest in size and was restricted to women. Second, the study measure of mood was limited to the scale developed from the POMS by Guadagnoli and Mor (1989). This scale has not been widely used; and the negative mood scale may suffer from floor effects, as 22 subjects had no negative mood on two consecutive days. Third, the immune assessments in the study were limited to CBC with differential count and NKCA; generalizability to other aspects of immune function cannot be assumed. Fourth, we cannot rule out the possibility that the observed relations between mood and NKCA may have been secondary to a number of unassessed psychosocial mediating variables. For example, individuals with more social support have been reported to have higher levels of positive mood (Cohen and Wills, 1985), and independent studies have found that social support is associated with higher NKCA (Baron, Cutrona, Hicklin, Russell, and Lubaroff, 1990). Positive mood may also be related to humor, which has been reported to have effects on immune function (Lefcourt, Davidson-Katz, and Kueneman, 1990; Edwards and Cooper, 1988; Martin and Dobbin, 1988; Dillon, Minchoff, and Baker, 1985). Fifth, differences in positive and negative emotions may reflect underlying personality differences. For example, several studies have found that negative mood is strongly related to neuroticism whereas positive mood is related to extraversion (Costa and McCrae, 1980). Based on the present results, further research with a larger sample of both men and women, with additional measures, assessed at multiple time points is clearly warranted. The initial evidence from the present study, consistent with the buffering hypothesis of positive mood, highlights the importance of further research in this area.

It remains to be determined whether the influence of positive mood on immune function will predominantly be due to effects on putative neuroendocrine pathways, which may affect either the number of NK cells in circulation or the functional activity of each cell (Whiteside and Herberman, 1994). Alternatively, the effects of positive mood on NKCA may be due to more indirect influences having an impact on coping mechanisms (Brown, Sirota, Niaura, and Engebretson, 1993; Edwards and Cooper, 1988). Regardless of the mechanisms responsible, the present study suggests that the assessment of positive mood may make an important contribution to future studies of psychological influences on immune function. As natural killer cells are thought to play an important role in cancer as well as in defense against infectious disease (Biron, 1994; Whiteside and Herberman, 1994), it will be important for future research to examine the possibility that these influences of mood may have clinical significance.

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Appendix D

Psychosocial Factors and Secretory Immunoglobulin A

Manuscript Accepted for Publication

Psychosocial Factors and Secretory Immunoglobulin A

Heiddis B. Valdimarsdottir
Memorial Sloan-Kettering Cancer Center
New York, NY, 10021

Arthur A. Stone
Department of Psychiatry and Behavioral Sciences
SUNY, Stony Brook, New York, 11794

Corresponding Author:
Dr. Heiddis B. Valdimarsdottir
Department of Psychiatry
Memorial Sloan-Kettering Cancer Center
1275 York Avenue,
New York, New York, 10021 USA
Tel: (212) 639-3279
E-mail: Valdimah@.MSKCC.org

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Abstract

This review focuses on studies that have examined the relation between psychosocial factors and secretory immunoglobulin A (s-IgA). Several studies have examined the relation between s-IgA and stressful circumstances ranging from major life events to minor daily events. The findings from these studies were often contradictory as different experimenters reported different stress-related changes in s-IgA. The effects of stress reduction interventions, such as relaxation and imagery, on s-IgA levels have also been examined. Although these studies indicate that various interventions are associated with increases in s-IgA levels methodological refinements are needed before more definitive conclusions can be made. The possibility that the relation between stress and s-IgA may be moderated by personality characteristics or mediated by psychological distress was supported in some studies. The review concludes with suggestions for future research.

Key words: Psychoneuroimmunology, Secretory Immunoglobulin A, Distress, Emotions, Stress

Introduction

In the late 1970's behavioral medicine was defined as a discipline that would investigate the interplay between psychological factors and somatic health and disease (Schwartz & Weiss, 1978)[1]. Of course, movements exploring closely associated topics, such as the psychosomatic medicine movement, predated and formed the groundwork for behavioral medicine. Interest in behavioral medicine has grown tremendously, spawning a number of societies and well over a dozen specialized journals.

As behavioral medicine research grew, research efforts shifted from the initial step of demonstrating relations between psychological or social factors and somatic outcomes to hypothesizing about and testing mediational pathways responsible for the observed associations. There are many models that have been proposed that summarize these relations (see reviews by Krantz, Grunberg, & Baum, 1985; Andersen, Kiecolt-Glaser, & Glaser, 1994), one of which was advanced by Cohen and Williamson (1991). According to this model, after an environmental stimulus has occurred (e.g., loss of job), has been appraised (e.g., as threatening to one's well-being), and after an affective response has occurred (e.g., negative mood or depression), a series of behavioral and biological processes may come into play. One of these processes is change in behaviors potentially related to disease. For instance, increased use of alcohol or illicit medications, changes in eating patterns, reduced exercise, and less or poorer sleep have all been shown to relate to stress. One of the biological processes that may be affected by the preceding events is the autonomic nervous system. Changes in sympathetic and parasympathetic tone are related to numerous hormonal changes that are likely to influence susceptibility to disease. The process that is the focus of this review is the immune system. Of course, this system is responsible for keeping pathogens out of the body and for eliminating them once they have entered.

Given the importance of the immune system for health, it is not surprising that scientists with an interest in behavioral medicine have targeted behavior--immune interactions. The extent of this focus is indicated by the creation of the discipline know as Psychoneuroimmunology (PNI). Several major texts have reviewed the PNI literature, there are societies devoted to the topic, and at least one journal publishes PNI work exclusively.

The work we discuss in this review falls into the domain of PNI and focuses on studies that have examined the relation between psychosocial factors and secretory immunoglobulin A (s-IgA). We first present an overview of s-IgA, followed by a discussion of the measures that have been used to index its activation. Summaries of the substantive work follows and is organized according to the nature of the psychosocial factors that have been manipulated or associated with s-IgA measures. These include stressful circumstances, relaxation and imagery, and psychological characteristics of the individual. A section on the possible mediational role of emotions, serving as a link between psychological factors and s-IgA follows. A section on future directions for examining the relation between psychosocial factors and s-IgA concludes this review. The studies

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[1] Other definitions have not explicitly excluded psychiatric disease from the definition. The first definition probably needed to do that to establish a clear boundary between tradition clinical psychiatry and psychology.

that were included in this review were identified by computerized search (Medline and PschLit) and by inspection of reference lists from existing reviews and articles.

Secretory Immunoglobulin A

A glycoprotein, called immunoglobulin A or IgA, is the major immunoglobulin class in the fluids that bathe the mucosal surfaces of the body and at those surfaces that are the paths of entry of invading bacteria and viruses into the body (e.g. tears, saliva, gastrointestinal, vaginal, nasal, and bronchial secretions [Tomasi, 1970; Tomasi, 1976; Goldblum, 1990]) Secretory IgA (s-IgA) is different from IgA in serum in that it is much larger (Tomasi, 1976) and probably binds invading organisms more effectively than serum IgA. Most infectious agents enter the body through the mucosal surfaces, and the presence of s-IgA antibodies in the fluids help to prevent infection, especially of the upper respiratory, intestinal, and urinogenital tracts (Tomasi, 1976; Lamm, Nedrud, Kaetzel, & Mazanec, 1995). For example, studies have shown that s-IgA antibody possesses antiviral activity (Dowdle, Coleman, Schoenbaum, Mostow, Kay, & Hierholzer, 1971; Lamm, Nedrud, Kaetzel, & Mazanec, 1995) and can prevent invasion by polio, measles, and rubella viruses (Ogra, Kee-Grant, Umana, Dzierba, & Weintraub, 1971; Ganguly, Ogra, Regas, & Waldman, 1973). In addition, there is evidence that s-IgA can prevent bacterial infections (Heddle & Rowley, 1975) and neutralize bacterial toxin (Waldman, Small, & Rowe, 1971; Goldblum, 1990). Secretory IgA is also implicated in dental diseases (Taubman & Smith, 1993). Degradation of s-IgA was associated with localized juvenile periodontitis (Gregory, Kim, Kindle, Hobbs & Lloyd, 1992). Similarly, caries-prone persons have been found to have lower salivary IgA concentrations than caries-resistant persons (Lehner, Cardwell, & Clarry, 1967; Gregory et al., 1992), and deficiencies in s-IgA have been identified as one of the factors responsible for the frequent oral infections in patients with AIDS (Muller, Holberg-Petersen, Rollag, Degre, Brandtzaeg, & Froland, 1992).

Measurement of s-IgA in Psychoneuroimmunology Studies

The two most commonly used measures of IgA production in the field of Psychoneuroimmunology have been s-IgA *concentration* and s-IgA *secretion rate*. Secretory IgA concentration is the amount of total IgA protein which is present in a certain volume of saliva (i.e., ug/ml) whereas s-IgA secretion rate refers to the amount of IgA protein detected per unit time (i.e., ug/min).

Although these measures have been used rather frequently in conjunction with psychosocial factors (as will be shown below), questions have been raised about their value as an index of immune system functioning. Stone, Cox, Valdimarsdottir, & Neale (1987) discussed several potential problems with measures of s-IgA concentration and secretion rate including: the effect of saliva flow rate on concentration; a possible deterioration of s-IgA proteins by proteases in the mouth; and, on a conceptual level, the meaning of total s-IgA protein as a measure of immune protection. Jemmott and McClelland (1989), who are the authors of the majority of the studies discussed in the Stone et al's. (1987) paper, replied in a subsequent paper. They argued that salivary flow rate might not be as large a problem, especially in unstimulated collection conditions, that the studies were consistent in the relation of s-IgA changes to psychological factors, that s-IgA might not deteriorate in the mouth, and that total s-IgA protein was shown to be a reasonable

measure.

Because these are debated issues (and because we have taken a position on some of these issues), we recommend readers to evaluate the arguments for themselves. However, we would like to comment briefly on the saliva flow issue. As stated above, one of the potential problems with using s-IgA measures is that saliva flow can affect both concentrations of s-IgA and s-IgA secretion rate. At least in some situations, it has been demonstrated that when saliva flow rate is artificially stimulated (with, for example, lemon drops), s-IgA concentrations decrease with increased flow while IgA secretion rate increases with increased flow rate (Brandtzaeg, 1971). Similar findings have been observed when saliva flow was not artificially stimulated (Evans, Bristow, Hucklebridge, Clow, & Walters, 1993; Graham, Chiron, Bartholomeusz, Taboonpong, & La Brooy, 1988; Kugler, Hess, & Haake, 1992). The relations between saliva flow rate and s-IgA concentration and secretion rate is particularly important since autonomic arousal associated with stress or negative affect may influence saliva flow rate (Stone et al., 1987), although the directionality of the effects is uncertain.

An issue in this debate that has not received much attention concerns the measurement of saliva volume. In our experience, measuring saliva flow is not a straightforward task, and we question the reliability as well as the validity of such measurement. Having a subject drool into a vial is difficult and we speculate that the amount of saliva collected is related to a number of factors concerning how the subject accomplishes the task. We know of no test-retest data demonstrating that flow is a reliable measure. This is an area that deserves some attention in the future.

On conceptual grounds, an alternative to the measurement of all s-IgA protein in a sample of saliva has been proposed by Stone et al. (1987). They argue that the s-IgA antibody response to a particular antigen be evaluated rather than s-IgA protein. One of the antigens that Stone and his colleagues have used in their studies is a harmless protein, rabbit albumin. According to these authors, the antibody responses to a novel antigen (e.g., rabbit albumin in samples of individuals who have not previously eaten rabbit) are analogous to those responses to a pathogen that would occur if an individual were infected by a virus or a bacteria.

To date, there has been no confirmation of the relative merits of the use of total s-IgA versus specific s-IgA antibody to a known antigen as only the Stone research group has employed the latter methodology. Jemmott and McClelland (1989) have raised issues concerning this measure given that it is based on a ratio of specific antibody to total s-IgA protein. Those authors are concerned that the overall amount of s-IgA is the important factor rather than the relative growth of s-IgA antibody. As will be shown below, there are many studies that have shown associations between psychological stressors or other conditions and s-IgA levels, and there have been two separate studies that shown such associations with s-IgA antibody to a novel antigen. In those studies, both measures of s-IgA were available and the specific antibody measure demonstrated stronger associations with stress variables than did the total protein measure. Nevertheless, no data are available that address the issue of which is a better empirical predictor of health status.

Stressful Events

Stressful events, ranging from major life events to daily events, have been shown to be

related to illness onset in a number of studies (Cohen & Williamson 1991). From the perspective of understanding the role of s-IgA, it is important to note that some of these studies had upper respiratory illness (URI) as the outcome variable. These studies support the idea that life stressors may be related to immunological processes, although compelling arguments can also be advanced that behavioral factors, such as sleeping, alcohol consumption, smoking, etc., also mediate the stress--illness association (see Cohen, Kessler, & Gordon, 1995). Several studies, reviewed below, examined the possibility that stressful life events (major and daily) affect s-IgA..

Total Event Studies. We start with studies that have used event checklists and created predictor variables representing the total amount of stress associated with those events an individual experiences. In general, studies have not found a relation between major life events (e.g., death of a spouse) and s-IgA (Kiecolt-Glaser, Garner, Speicher, Penn, Holliday, & Glaser, 1984; Graham et al., 1988) or between daily hassles (defined as minor daily annoyances, but which are usually measured in a retrospective manner over a 30-day period [see Kanner, Coyne, Schaeffer, & Lazarus, 1981]) and s-IgA (Kubitz, Peavey, & Moore. 1986; Farne, Paola, Corallo, Gnugnoli, & Sacco, 1994). A complex relation between s-IgA concentration and daily hassles was observed in Martin's and Dobbin's (1988) study of daily hassles. In this study, hassles and s-IgA were assessed during two sessions 90 days apart. Frequency of hassles assessed during the first session was negatively correlated with s-IgA concentration assessed in both sessions. On the other hand, no relation was observed between frequency of hassles and s-IgA concentration assessed during the second session.

Two studies have examined how minor stressors measured on a daily basis affect s-IgA. In Evans's and Bristow's (1993) study, subjects completed the Student's Assessment of Daily Experience (SADE) questionnaire daily for 14 days. Each of the 27 events on the SADE that occurred during the day was rated by subjects on a 6-point scale from "extremely desirable" to "extremely undesirable". On each day subjects also provided a timed saliva sample for assessments of s-IgA concentration and s-IgA secretion rate. When the data was aggregated over the two-week period, a negative correlation was observed between undesirable events and s-IgA concentration and a positive correlation was observed between desirable events and s-IgA concentration. That is, the mean level of s-IgA concentration across all days was negatively correlated with the average number of undesirable events for the same period and positively correlated with the average number of desirable events. A parallel finding was observed for s-IgA secretion rate. On the other hand, analyses examining the day-to-day association between events and s-IgA concentration and secretion rate (within-subjects as opposed to the previous between-subjects analyses) revealed that while undesirable events were associated with higher concentrations of s-IgA, undesirable events were unrelated to s-IgA secretion rate. Desirable events were unrelated to both s-IgA concentration and s-IgA secretion rate. These findings are troublesome since the two types of analyses produced divergent results.

In contrast to the Evan's study of total s-IgA, Stone, Neale, Cox and colleagues (1994) employed the specific antigen model of s-IgA. They exposed 94 adult males to a harmless protein (rabbit albumin) and examined whether daily events affected s-IgA antibody response to the rabbit albumin. The immunization procedure involved daily ingestion of a capsule containing rabbit albumin for 12 weeks. Each day, subjects also completed a 80-item event checklist which was organized in sections dealing with work, leisure, friends, spouse, children, household activities,

finances, self, and two write-in items. A further refinement of the event assessment was that subjects' spouses aided them in the accurate completion of the event checklist to ensure the most accurate, objective reports of daily events (see Stone & Neale 1982 for a description of the questionnaire development). To assess the subjective experience of the event, each event that occurred during the day was rated on a 6-point scale from extremely desirable to extremely undesirable.

After completing the questionnaire, subjects collected saliva which was assayed for s-IgA antibody activity to the rabbit albumin. Results from within-subject analyses revealed that the frequency of desirable events was related to more s-IgA antibody production whereas the frequency of undesirable events was related to less s-IgA antibody production. In other words, on days when there were relatively more undesirable events than usual, s-IgA antibody levels were lower than on days without undesirable events. The authors also examined whether daily event content predicted s-IgA antibody production. Undesirable work events and desirable leisure and household events were more strongly related to-IgA antibody than events in other categories. Lastly, desirable events on previous two days predicted subsequent increase in s-IgA antibody production but for undesirable events only the same-day events inversely predicted s-IgA antibody production. It is important to note that days with upper respiratory symptoms were eliminated from these analyses; this has not been done in other daily studies.

Single Event Studies. Rather than investigating how the number of major stressful life events or day to day events affect s-IgA several studies have examined the impact of a single stressful circumstance, academic pressure due to examinations. Two studies reported that academic stress is associated with reductions in s-IgA. Jemmott, Borysenko, Borysenko, McClelland and colleagues (1983) collected saliva from 47 dental students. Five collections were made over an 11 month period: three collections were made during examination periods and 2 during low-stress periods. The authors found that s-IgA secretion rate was lower during the 3 exam points compared to the 2 low-stress points. As data collection was spread over an 11 month period it is possible that these effects were due to seasonal variation in s-IgA secretion. To rule out this possibility, Jemmott and Magloire (1988) conducted a second study using a shorter time interval. Saliva was collected from 15 undergraduates five days prior to their exam, during their exam period, and two weeks after their exam. S-IgA concentration, s-IgA secretion rate, and s-IgA statistically adjusted for saliva flow were lower during the exam period compared to the measures collected before and after the exam.

Increases in s-IgA have also been observed after examination. McClelland, Ross, and Patel (1985) found that both s-IgA concentration and norepinephrine concentration in saliva increased in 46 students both immediately after and 1 3/4 hours after an exam, compared to baseline measures collected several days after the exam. The increase in norepinephrine concentration did not account for the increase in s-IgA concentrations as the correlation between these two measures was nonsignificant. Evans and colleagues (1993) collected saliva from 18 students in two consecutive weeks, in the second week all students had to give a presentation. During both weeks saliva was collected 4 times one hour apart, and in the second week saliva was collected immediately after the presentation. The authors found that there was a trend ($p = .10$) for s-IgA secretion rate to increase from week 1 to week 2 to post-presentation. A parallel increase was observed in salivary cortisol concentrations. However, as the authors did not examine the relation

between s-IgA secretion rate and salivary cortisol, it is not clear if the increase in salivary cortisol contributed to the increase in s-IgA secretion rate.

No change in s-IgA following an examination has also been observed. Kiecolt-Glaser and colleagues (1984) collected saliva from 65 medical students a month before a final exam and again on the first day of final exam. No change in s-IgA concentration was observed from pre-test to post-test assessments. Mouton, Fillion, Tawadros and Tessier (1989) collected saliva from 44 dental students on four occasions over 2 academic years: two collections were made during a low-stress periods and two collections were collected during examination periods. Results indicated that academic examination affected s-IgA secretion rate only when the final examination and the summer vacation samples were compared (s-IgA secretion rate was lower during the final examination than during the summer vacation). On the other hand, no difference in s-IgA secretion rate was observed from samples collected during midterm exam to samples collected during midterm break.

Summary. The pattern of results in these studies is neither consistent nor simple. Many studies that examined major life events and daily hassles used retrospective designs in which subjects indicated how many life events or hassles had occurred over a prior time period. It is therefore possible that recall ability and/or memory biases accounted for the lack of association between s-IgA and life events. The studies that examined the impact of academic stressors on the secretory IgA are difficult to evaluate because they differ on several key variables. One of these variables is the timing various experimenters chose to collect their pre-stress, stress, and post-stress measures. For example, McClelland et al. (1985) collected baseline measure a few weeks after the exam and stress measure immediately after an exam and 1 3/4 hours after the exam whereas Jemmott et al. (1988) collected their baseline measure 5 days prior to the exam and the stress measure during the examination period. Certainly it is possible that changes in secretory IgA observed at some of these times might not be present at other times. It is of interest that the two studies (McClelland et al., 1985; Evans et al., 1994) that observed increases in s-IgA following the academic stressor collected their stress measures immediately following the completion of the exam. It is possible that termination of an acute stressor results in increased s-IgA, however, before any conclusion can be reached, studies need to be conducted which will allow definite observation of timing factors.

Another variable on which these studies differ is the procedure used to determine s-IgA. McClelland et al. (1985), for example, measured s-IgA concentration whereas Mouton et al. (1984) measured s-IgA secretion rate. Only two of the studies (Mouton, et al.,1989; Jemmott & Magloire 1988) measured saliva flow rate. Examination stress has been found to affect flow rate (Bates & Adams 1968) and as discussed above, s-IgA concentrations and secretion rate are differentially affected by saliva flow rate. Therefore, it is difficult to interpret the findings that did not take saliva flow rate into account as the effects of stress on saliva flow could have accounted for the changes observed in s-IgA.

The mechanism whereby stressful events affect s-IgA is not clear. It has been hypothesized that stress affects the immune system through it's impact on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (see review by Rabin, Cohen, Ganguli, Lysle, & Cunnick. 1989; Adler, Cohen & Cohen, 1995; Weigent & Blalock 1995; Bedovsky & Rey 1996). In the studies reviewed above changes in salivary cortisol (Evans et al., 1994) and in salivary

norepinephrine (McClelland et al., 1985) were observed in parallel to changes in s-IgA levels. However, it is not clear if these stress-induced hormonal changes contributed to the stress-induced changes observed in s-IgA levels as McClelland et al. (1985) found no relation between salivary norepinephrine concentration and s-IgA concentration and Evans et al. (1994) did not examine the relation between salivary cortisol concentration and s-IgA secretion rate.

Relaxation and Imagery

The evidence that stress can affect the immune system, including s-IgA, raises the possibility that positive experiences, the opposite of stressful ones, could also affect the activity of the immune system (see review by Van Rood, Bogaards, Goulmy, & Van Houwelingen, 1993; Jasnoski & Kugler, 1987; Zakowski, Hall, & Baum, 1989). Several behavioral intervention techniques have been found to influence physiological processes, such as heart rate and blood pressure (Basmajian, 1989; Blumenthal & McKee, 1987) . The studies reviewed below examined whether it is possible to increase the levels of s-IgA by stress-reducing interventions.

Green and Green (1987) randomly assigned 50 college students to relaxation groups (relaxation response, guided visualization, back massage) or control groups (lying quietly with eyes closed or touching-control group). Saliva samples were collected before and immediately after the session which lasted 20 minutes. Results indicated that there was a significant increase in s-IgA concentration from pre to post treatment in the relaxation groups but no change was observed in the control groups. Salivary cortisol was not affected by the relaxation training, suggesting that the changes in s-IgA were independent of changes in cortisol.

In another study, the same authors (Green, Green, & Santoro, 1988) examined the effect of daily relaxation on several parameters of the immune system, including s-IgA secretion rate. Forty subjects were randomly assigned to practice one of three relaxation techniques (relaxation response while sitting up, relaxation response while lying down, and guided visualization while lying down) daily for three weeks. Saliva samples were collected before and after 20 minutes of supervised relaxation on day 1 and on day 22 or after three weeks of practicing the relaxation. As there were no differences among the relaxation groups the data from the three treatments were combined. Confirming previous finding, a significant increase in s-IgA secretion rate was observed immediately after 20 minutes of relaxation practice compared to levels right before the relaxation. In addition, long-term practice effects were also observed: s-IgA secretion rate increased significantly from day 1 to day 22. These changes in s-IgA secretion rate appeared to be independent of psychological distress as no change was observed in anxiety as measured by the anxiety scale on the Hopkins symptom checklist (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974) and the Taylor manifest anxiety scale (Taylor, 1951).

Jasnoski and Kugler (1987) randomly assigned 30 undergraduates to two relaxation groups or a control group. One of the relaxation groups was trained in progressive relaxation and focused breathing while the other relaxation group was also trained in imagining powerful, positive immune function. The control group was instructed to discriminate between two tones presented at variable intervals. Saliva samples were collected before and immediately after the training sessions. After a single one hour session an increase was observed in s-IgA in both of the relaxation groups but no change was observed in the control group. Norepinephrine and epinephrine from saliva and serum were also assessed as well as cortisol in saliva. However, none

of these neuroendocrine measures accounted for the s-IgA difference between the relaxation and the control groups.

Rider, Achterberg, Lawlis et al. (1990) examined whether imagery directed at biological mechanisms is more effective in increasing s-IgA concentration than nondirected imagery. Forty-five students were randomly assigned to 3 groups. Group 1 was instructed to focus their imagery on their immune system while they listened to an audio cassette containing imagery instruction followed by music. Group 2 received the same music and general nonspecific imagery instructions, and Group 3 underwent no treatment. Subjects came for 3 sessions scheduled 3 weeks apart (day 1, 21, and 42) and each session lasted 17 minutes. Saliva samples were collected at the beginning of each session and again at the end of each session. Subjects in the treatment groups were provided with cassette tapes which they were instructed to listen to at home on a bi-daily bases for six weeks.

In both treatment groups s-IgA concentration increased within each session, yet no change was observed in the control group. Changes in s-IgA concentration across the sessions was not examined, however, inspection of the means suggest that the treatments did not increase s-IgA across sessions. The interventions decreased psychological distress as measured by the Profile of Mood States (McNaire, Lorr, & Droppleman, 1971) but no change was observed in sympathetic nervous system response as measured by skin temperature. The treatment groups reported fewer symptoms during the study, however, the particular symptoms affected did not appear to be immune related (breathing difficulty, jaw clenching and rapid heartbeat). In their second study, Rider & Welden, 1990 used live, improvised music instead of taped music and only one 10-minute session was conducted. After the intervention, concentrations of s-IgA were higher in the music+imagery group than in the music only group and in the control group. The music only group did not differ from the control group.

One study has examined whether relaxation affects s-IgA in children. Olness, Culbert and Uden (1989) assigned 57 children to two treatment groups and a control group. During the treatment session, which lasted 25 minutes, both treatment groups learned self-hypnosis, in addition, one of the groups were given specific suggestions about increasing salivary immunoglobulins. The control group subjects were engaged in conversation for 25 minutes. Children who received the specific suggestion had significantly higher concentrations of s-IgA after the training session. No change was observed in the other two groups.

Groer, Mozingo, Droppieman et al. (1994) examined the effects of a 10-minute nursing back rub on s-IgA concentration and s-IgA secretion rate. Eighteen subjects who were assigned to the experimental group received a 10-minute back rub and 14 subjects who were assigned to the control group rested for 10-minutes. Although the treatment did not affect anxiety as measured by the Spilberger state/trait anxiety inventory (Spielberger, 1983), an increase in s-IgA concentration was observed in the experimental group and a similar trend was observed for s-IgA secretion rate.

Summary. These studies suggest that various interventions can induce short-term increases in s-IgA levels. However, methodological refinements are needed before more definitive conclusions can be made. The long term effects of these interventions on s-IgA levels are not clear as most of the studies only collected saliva immediately before and immediately after the intervention. Of the two studies (Green et al., 1988; Rider et al., 1990) that assessed s-IgA few

weeks after their intervention, only one (Green et al., 1988) reported an increased levels of s-IgA as long as 22 days after the completion of the intervention. Furthermore, future studies need to assess variables such as frequency of practice and compliance with treatment regimens. Because none of the studies assessed whether the individuals used relaxation skills in stressful situations, there is no experimental evidence that coping (e.g., relaxation) intervenes between stress exposure and s-IgA.

The mechanism whereby these interventions affect s-IgA is not yet clear. It is possible that these interventions affect subjective distress and physiological arousal which in turn may affect s-IgA. However, of the three studies (Green et al., 1988; Rider et al., 1990; Groer et al., 1994) that assessed subjective distress only one study (Rider et al., 1990) observed a decrease in subjective distress after the intervention and the two studies (Green & Green, 1987; Jasnoski & Kugler, 1987) that included neuroendocrine assessments did not observe changes in these measures following the intervention. Clearly, studies are needed that systematically investigate the mechanism underlying the effects of psychosocial interventions on the s-IgA.

One possible confounding in these studies is saliva flow rate. Relaxation has been found to affect saliva flow rate (Carlson, 1986) and saliva flow rate can affect both s-IgA concentration and secretion rate. As none of the studies corrected their s-IgA measures for flow rate the possibility that the change in secretory IgA was due to flow rate changes can not be ruled out.

Psychological Characteristics of Individuals

In earlier reports on the relationship between stress and illness it was assumed that stressors impacted similarly on all individuals. However, as the correlation between stressful life events and illness was found to be generally low, researchers became more interested in moderating and/or mediating variables that might augment or reduce the effects of stressful variables. The studies reviewed below have examined the possibility that variables which have been shown to moderate the stress and illness association also moderate the relation between stress and s-IgA concentration and secretion rate.

Sense of humor. This has been found to moderate the relation between stressful life experiences and psychological distress Lefcort and Martin (1986). The possibility that sense of humor may also affect s-IgA has been examined in several studies. Martin and Dobbin (1988) examined whether sense of humor moderates the effects of daily hassles on s-IgA concentration. Approximately 90 days apart, 40 undergraduates provided saliva samples and completed a daily hassles scale. In addition, they completed four humor questionnaires (situational humor response, coping humor, sense of humor, and liking of humor). Sense of humor was unrelated to s-IgA concentration, but there was some support for the stress-buffering effects of humor: the negative association between hassles assessed at time 1 and s-IgA concentration assessed at time 2 was stronger for individuals with low scores on the humor questionnaires than for individuals with high scores on the humor questionnaires.

Another way that humor has been explored is shown in an investigation of exposure to humorous stimuli in individuals with good sense of humor. Dillon and Baker (1985) observed an increase in s-IgA concentration among 10 subjects immediately after they had watched a humorous videotape but not after they had watched a didactic control tape. Change in s-IgA was inversely related to sense of humor as measured by the Coping Humor Questionnaire (CHQ:

Martin & Lefcourt, 1984). On the other hand, in contrast to Martin and Dobbin's (1988) finding, baseline levels of s-IgA was positively related to sense of humor. Similarly, Dillon and Totten (1989) who studied 17 women before and after they gave birth found a positive association between s-IgA concentration and sense of humor as measured by the CHQ.

Lefcourt, Davidson-Katz, and Kueneman (1990) conducted three studies to examine the relation between sense of humor, humorous stimuli, and s-IgA. In all three studies, subjects watched humorous movies and provided saliva samples before and after the presentation of the movies. The movie presented and methods to assay s-IgA along with the timing of baseline assessments varied between the studies. In all three studies, subjects completed two humor scales, the Situational Humor Response Questionnaire (SHRQ:Martin & Lefcourt 1984), and the Coping Humor Scale (CHS: Martin et al., 1993). There was an increase in s-IgA from before to after the presentation of the humorous move in all three studies. None of the studies found a relation between sense of humor and baseline levels of s-IgA. Subjects who scored high on the CHS in study 1 had a significant increase in s-IgA concentration whereas no change was observed among subjects who scored low on the this scale; this relation was not observed in studies 2 and 3. A marginally significant interaction was found in study 3 between SHRQ and condition which reflected the greater change for subjects with high SHRQ scores; this interaction was not observed in studies 1 and 2.

Two studies examined the effects of weeping and laughing on s-IgA. Labott, Ahleman, Wolever et al. (1990) showed 32 undergraduate women sad and humorous videotapes. Half of the subjects were told to express their emotions and half of the subjects were told to inhibit their emotions. Seven control subjects watched documentary tapes. Seven subjects in the expression condition were excluded from the analyses as they failed to overtly express their emotions and seven inhibition subjects were excluded as they overtly expressed their emotions. Individuals who cried during the sad movie had significantly lower s-IgA concentration after the movie compared to both the control subjects and the subjects who inhibited overt expression of crying. On the other hand, the humorous move was associated with increased s-IgA concentration regardless of the expression or inhibition of overt laughter. Sense of humor, as assessed by the Coping Humor Questionnaire (Martin & Lefcourt 1983) was not associated with initial or baseline s-IgA concentration values. To further examine the effects of emotional crying on s-IgA concentration Martin, Guthrie and Pitts's (1993) showed 42 undergraduates a sad movie. An increase was seen in s-IgA from pre to postmovie in subjects who reported that they had not cried during the movie. No change was seen in s-IgA among subjects who reported that they had had tears in their eyes during the movie or among subjects who reported that they had tears down their face or sobbed during the movie.

Inhibited and stressed power motivation. These concepts have been studied extensively by David McClelland and his coworkers. Individuals high in inhibited power motivation are assertive and hard driving, but inhibited in direct expression of aggression. Such people are more vulnerable to disease than others, especially if they have experienced or are currently under power related stress (i.e., life events which challenge or threaten the individuals ability to perform powerfully or impress others). In a series of studies, McClelland and colleagues have examined power motivation and s-IgA.

McClelland, Floor Davidson and Saron (1980) explored the relation between power

motivation, stressful life events, upper respiratory infection and concentrations of s-IgA. Twenty-seven male college students were assessed twice 48 to 72 hours apart. During the first session, subjects provided saliva samples and completed a modified version of the Social Readjustment Rating Scale (SRRS: Holmes & Rahe, 1967) and an illness inventory. The items of the SRRS were classified as power events, affiliative events, both, or neither. During the second visit, subjects provided urine samples for assessments of epinephrine and norepinephrine, after which they participated in a mildly stressful task for 2 1/2 hours, followed by additional urine and saliva sampling. Seven subjects were classified as high in need for power, high in inhibition, and high in reported power stress (HHH group). The HHH subjects reported more illnesses in the past 6 to 10 months, had lower s-IgA on the first assessment, and had higher epinephrine excretion rates (assessments before and after the task were averaged) than other subjects. On the other hand, the HHH subjects did not differ from other subjects in norepinephrine excretion rate or in the concentration of s-IgA after the task.

In a similar study with 133 prisoners, McClelland, Alexander and Marks (1982) found that prisoners that scored high on need for power and high on life stress had a lower concentration of s-IgA and reported more illnesses in the past 12 months. In contrast to their 1980 study, prisoners who were also high on inhibition had higher concentrations of s-IgA and reported fewer illnesses in the past 12 months than prisoners low on active inhibition.

In two of the examination studies reviewed above, McClelland and coworkers, investigated whether examination stress had greater impact on s-IgA among students high in need for power. The first study (Jemmott et al., 1983) assessed s-IgA secretion rate 5 times (3 exam points and 2 low-stress points) over a 11 month period. A continuing decline in s-IgA secretion rate through the final low-stress period was observed among the students classified as high in need for power and high in active inhibition whereas s-IgA secretion rate recovered during the low stress periods in all other subjects. Moreover, students classified as high in need for affiliation and low in active inhibition had higher s-IgA secretion rates on all 5 assessments compared to all other students. In their second study McClelland et al. (1985) failed to find a consistently higher s-IgA levels among individuals classified as high in need for affiliation. A difference in s-IgA concentration was observed after taking an exam between individuals who differed on power motivation: Students whose need for power was stronger than their need for affiliation had lower s-IgA one and three-quarter hours after their exam as compared to both baseline measures collected a few days after the exam and to students whose need for affiliation was higher than their need for power. Students with stronger need for power also had greater increases in norepinephrine in response to the examination but increase in salivary norepinephrine was not related to s-IgA concentration.

Locus of control. This concept is defined as a person's belief that they can control desired or undesired outcomes (such individuals have an internal locus of control) or that such outcomes are the results of fate, luck or other forces (external locus of control). Kubiz et al. (1986) examined the relation between health locus of control, daily hassles and levels of s-IgA concentration. Twenty-nine subjects provided saliva samples, and completed both the Multi-Dimensional Health Locus of Control Scale (MHLC; Wallston, Kaplan, & Maides, 1976), a measure of locus of control over health outcomes, and the Hassles Scale (Kanner et al., 1981), a measure of frequency and intensity of stressful situations in the past month. The results indicated

that while there was no relation between levels of s-IgA concentrations and daily hassles there was an inverse relationship between concentrations of s-IgA and internal locus of control. An interaction between locus of control and daily hassles was also obtained: individuals high on internality and with high levels of daily hassles had lower levels of s-IgA than individuals low on internality and with high levels of daily hassles. As discussed by authors, the finding that subjects with more internal locus of control had lower levels of s-IgA was surprising as several studies have shown that internally oriented individuals report fewer illnesses (Wallston & Wallston, 1982). Lastly, menstrual cycle status may influence levels of s-IgA as higher levels of s-IgA was observed for female subjects in their first half of their cycle than for females subjects in their second half of their cycle.

Hardiness. This concept has been defined as a composite of three tendencies: sense of internal locus of control, sense of purpose and involvement, and a tendency to view changes as incentives or opportunities for growth (Kobasa, 1979; Kobasa, 1982). Several studies have shown that hardiness plays an active role in protecting individuals from stress (Kobasa, 1979; Kobasa, Maddi, & Courington, 1981; Kobasa, 1982). In Dillon et al's study (1989), reviewed above, hardiness was not related to s-IgA concentration or to upper respiratory tract infection.

Social support. Among the variables discussed in this section of the paper, as having an association with health status, social support has by far received the most empirical support. Generally, the idea is that higher levels of social supports are related to positive health outcomes (Cohen & Wills, 1985), but there are more complex hypotheses as well. According to the main effect hypothesis, social support is beneficial for health regardless of whether the individuals are exposed to stress. Alternatively, according to the buffering hypothesis, social support has beneficial effects on health only when individuals are exposed to stress. Existing studies support both of these hypothesis (Cohen & Wills, 1985). The study by Jemmott and colleagues (1988), reviewed above, included a measure of social support. Consistent with the main effect model the authors found that students who reported adequate social support had higher concentrations of s-IgA across all three assessments (pre-exam, exam, post-exam). On the other hand, in contrast to the buffering hypothesis, the relation between adequacy of support and s-IgA concentrations did not differ in the exam period compared to the pre- and post-exam periods. Two of the studies reviewed above included measures of loneliness. In both studies loneliness, which may reflect low social support, was unrelated to s-IgA concentration (Kiecolt-Glaser et al., 1984) and to s-IgA secretion rate (Green et al., 1988).

Summary: Taken together, these studies, demonstrate that in order to maximize the predictive value of stress-immune function research, experimenters need to include potential moderators and mediators in their study designs. However, integrating and drawing conclusions from these studies is difficult for a number of reasons described below.

Sense of humor was one of the most examined personality variable. While humorous movies were consistently found to induce short-term increases in s-IgA, the results for sense of humor were inconsistent. Individuals who scored high on measures of sense of humor were found to be more responsive to comic material (Lefcourt et al., 1990); less responsive to comic material (Dillon & Baker, 1985); or respond the same way to comic material as individuals who scored low on sense of humor (Lefcourt et al., 1990). In addition, it is not clear if sense of humor is associated with higher levels of resting levels of s-IgA as some authors found a positive relation

(Dillon & Baker, 1985) while others reported no relation (Labott et al., 1990; Lefcourt et al., 1990). These contradictory findings may be due to the fact that the studies differed on several key variables including the measures used to assess sense of humor, movies selected to elicit humor and methods used to assay s-IgA.

Inhibited power motivation is another personality variable that has been extensively studied. All of these studies were correlational and as such do not address the issue of causality. Importantly, the findings were often inconsistent. Individuals who scored high on inhibition (in combination with need for power and power stress), for example, were reported to have lower levels of s-IgA concentrations in some studies (McClelland et al., 1980) yet higher levels of s-IgA concentrations were observed in others (McClelland et al., 1982). Moreover, high levels of affiliative need were found to be associated with higher levels of s-IgA secretion rate during both stress and non-stress periods (Jemmott et al., 1983), but this finding was not replicated for s-IgA concentration (McClelland et al., 1985). Again these discrepant results may be due to different subject populations used in these studies as well different methods used to assay s-IgA.

It is implied in all of these studies that individuals with different personality profiles differ in how they appraise and cope with the stressor they encounter. For example, individuals high in inhibited power motivation are expected to appraise and cope differently than subjects low in need for power. Thus consistency in coping across different situations and individuals is implied by these authors. However, the efficacy of using personality traits in predicting behavior has been challenged (Michel, 1968; Michel, 1973). In general, individuals are characterized more by variability than stability in coping (Folkman & Lazarus, 1980; Lazarus & Folkman, 1984). We found no direct evidence that coping affects or alters the stress-induced changes in s-IgA.

The finding by Jemmott and his colleagues (1988) that social support was associated with higher levels of s-IgA is interesting as several studies have demonstrated that social support is related to health outcomes. However, as this was the only study that examined the role of social support it is not clear if social support affects s-IgA regardless of whether the individual is undergoing stress or if it also buffers the effects of stress on s-IgA. Clearly, studies are needed that replicate and extend (i.e., manipulate social support) this finding.

The Mediational Role of Emotional Distress

The above studies lend some support for the hypotheses that stressors and psychobehavioral interventions can affect s-IgA. But how do stressors and psychobehavioral interventions result in s-IgA alteration? One possible pathway is that stressors and interventions affect psychological distress which in turn affect biological systems (i.e., nervous system, neuroendocrine system) that influence immunologic processes including s-IgA (see Stone, Marco, Cruise, Cox, & Neale, in press). Several of the studies reviewed above did not include measures of psychological distress and could not address this hypothesis. Those that did either found no changes in psychological distress or did not examine if changes in psychological distress mediated the changes in s-IgA levels. For example, one study (Rider et al., 1990) found that psychological distress was reduced after a psychobehavioral intervention and three studies (Jemmott et al., 1983; Mouton et al., 1989; Evans et al., 1994) found that academic examination increased psychological distress. However, as none of these studies examined the relation between changes in psychological distress and changes in s-IgA, there is no evidence that changes in s-IgA

observed after various interventions and stressors are mediated by changes in psychological distress.

The strongest support for the hypothesis that psychological distress mediates the relation between stress and s-IgA comes from Stone et al. (1994) described above. A recent analyses of that study's data (Stone et al., in press) employed analyses specifically designed to address third variable mediational questions. Results indicated that the negative relation between undesirable events and s-IgA antibody production was mediated by increases in negative mood and the positive relation between desirable and s-IgA antibody production was mediated by increases in positive mood.

Other studies have examined the impact of positive and negative affective states without an explicit stressor. Stone, Cox, Valdimarsdottir, Jandorf et al. (1987) examined the relation between daily fluctuations in mood and s-IgA antibody production. Throughout an 8-week period, 30 male dental students ingested a capsule daily, containing a purified rabbit albumin, and three times a week over the 8 week period they completed the Nowlis Mood Adjective Checklist (Nowlis, 1965) and provided saliva samples that were assayed for IgA antibody production to the albumin. Examination of s-IgA antibody responses showed that antibody response was lower on days with high levels of negative mood relative to days with low levels of negative mood. On the other hand, antibody production was higher on days with high levels of positive mood relative to days with low levels of positive mood. Stone et al. (1994) replicated their finding, positive affect was associated with higher levels of antibody production and negative mood was associated with lower levels of antibody production. As raised by the authors (Neale & Stone, 1989), one possible explanation for these findings is that negative daily events affect the fluctuation in mood which in turn suppresses s-IgA antibody production. This is an unlikely explanation as the authors found in one of their subsequent studies that the relationship between s-IgA antibody production and mood remained significant after controlling for daily events (Stone et al., in press).

In the Evans et al. (1993) study reviewed above, 12 subjects completed the Nowlis Mood Adjective Checklist and provided saliva samples daily for 14 days. No relation was observed between affect (positive and negative) and s-IgA concentration and secretion rate when the data was averaged across all days. On the other hand, within-subject analyses showed that s-IgA concentrations and secretion rate was higher on days with high levels of negative affect. Although not significant there was a trend for s-IgA concentration and secretion rate to be lower on days with high levels of positive affect.

Using a between-subjects analyses, Graham and colleagues (1988) found in their study of 114 nurses, that nurses that reported that they were frequently anxious had lower secretion rate of s-IgA than nurses who reported that they were "occasionally" anxious, but no difference was observed in s-IgA concentrations. Both s-IgA concentration and secretion rate were unrelated to depression as measured by one item (how often do you feel depressed) and to psychological distress as measured by the health questionnaire (Goldberg, 1972). It is possible that the anxiety-associated reductions in IgA secretion rates were due to the rate of saliva flow, which is under the autonomic control, rather than by direct influence on s-IgA secretion rate.

In the Green and colleagues (1988) study reviewed above no relation was observed between s-IgA concentration and subjective distress as measured with the Hopkins Symptom Checklist (Derogatis et al., 1974). Kugler Hess and Haake (1992) collected saliva and

administered a mood adjective checklist to eighty-four medical students. Of the 15 dimensions on their adjective checklist only excitement was positively related to s-IgA concentration.

Summary. Although relatively few studies have examined the relation between subjective distress and s-IgA, the above studies suggest that in order to understand the influence of the psychosocial environment on s-IgA future researchers should include measures of affect and subjective distress in their study design. Stone et al's (1987, in press) findings that both negative and positive affect mediated the relation between daily events and s-IgA antibody production indicate that researchers should not only focus on the role of negative affect but should consider the contribution of positive affect as well.

With the exception of the daily assessment studies the above studies assessed psychological distress or affect at one point in time and it was not clear what time frame was used. The reliability of subject recall is an issue in those studies that may have used a long time frame.

Conclusion and Future Directions.

It is clear that there is substantial evidence that psychosocial variables can affect secretory immunoglobulin A. It should also be evident that it is difficult to compare and draw definite conclusions from these studies as the studies differed on several key variables, including the duration and type of the stressors and interventions, timing of assessments relative to the stressors and interventions, and methods used to assay secretory IgA. The majority of the reviewed studies assessed concentrations of s-IgA without controlling for the amount of saliva collected during the sampling period. Therefore the possibility that the stress-elicited changes in s-IgA concentration were due to stress-induced changes in flow rate can not be ruled out. Secretory IgA secretion rate was assessed in some of the above studies and in some instances opposite patterns were observed for s-IgA secretion rate and s-IgA concentration. For example, McClelland et al. (1985) found that an examination stress increased s-IgA concentration whereas Jemmott et al. (1983) found that the same stressor decreased s-IgA secretion rate. Herbert and Cohen (1993), in their meta-analytic review, compared the results of studies that reported the concentration of s-IgA with those that reported the secretion rate. Their analysis showed that the association between stress and s-IgA concentration was significantly stronger than the association between stress and s-IgA secretion rate. Until more studies have demonstrated that psychosocial factors affect the s-IgA after controlling for salivary flow rate, results of s-IgA concentration have to be interpreted cautiously.

Studies that examined the relation between stressful events and s-IgA support the hypothesis that events are associated with reduced s-IgA. However, as all of these studies were correlational they do not address the issue of causality. The clinical significance of these stress-elicited changes in s-IgA is not yet known, and these alterations may reflect transient fluctuations within range of normal function. Some investigators assessed whether subjects had been sick in the months preceding their participation in the studies. McClelland and colleagues (1980, 1982) found some evidence that subjects who were high in need for power and high on power related stress had lower levels of s-IgA concentrations and reported more illnesses in the previous 12 months than other subjects. On the other hand, Graham et al. (1988) found no relation between s-IgA secretion rate and upper respiratory infection in the past 12 months. One difficulty with

interpreting these findings is that it is not clear if subjects were sick at the time that their saliva was collected for immune assessments which could affect s-IgA concentrations and secretion rate.

Stone and colleagues found (Stone et al., 1987; 1994) that stress interfered with the production of antibody responses to a novel antigen. These findings indirectly support the hypothesis that stress-induced changes in s-IgA may have clinical significance as the responses to the novel antigen may be analogues to those responses that would occur if the individual is exposed to a virus or a bacteria. Clearly longitudinal and experimental studies are needed to further examine the clinical impact of stress-induced changes in s-IgA.

The mechanism whereby stress affects s-IgA is not clear. It has been hypothesized that stress affects the activity of the immune system through it's impact on the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Several studies have demonstrated that these pathways are activated by stress which results in increased level of circulating catecholamine and cortisol. There is also accumulating evidence indicating that the immune cells have receptors for these hormones which supports the hypothesis that they are involved in immune modulation (See review by Rabin et al., 1989; O'Leary, 1990; Ader, Felten, & Cohen, 1991; Adler et al., 1995; Weigent & Blalock 1995; Bedovsky & Rey 1996) . Some of the studies reviewed above did assess catecholamine (McClelland et al., 1985; Kugler et al., 1992; 1993) and cortisol (Evans et al., 1994). Although changes in these hormones were observed in parallel to changes in s-IgA, it is not clear if these hormonal changes accounted for or contributed to the stress-induced changes in s-IgA as the investigators either found no relation between their hormonal measures and their measurers of s-IgA or the investigators did not examine if the immune changes were due to the hormonal changes. That is, mediational models of the observed relations were not tested. Thus, whether or not stress affects the activity of s-IgA through it's impact on neuroendocrine pathways has not been answered.

There is some evidence that psychological distress mediates the relation between stress and s-IgA. Stone and colleagues (in press) found that increases in negative mood mediated the negative relation between undesirable events and s-IgA antibody production and increases in positive mood mediated the positive relation between undesirable events and s-IgA antibody production. It is possible that behavioral responses account for the immune changes found in theses studies. There is evidence that health practices, such as smoking, amount of sleep, alcohol consumption can affect the activity of the immune system (Irvin, Smith, & Gillin, 1992; MacGregor, 1986, including s-IgA (Bennet & Reade, 1982). Until additional studies are conducted, that control for these health practices, the possibility that the stress-induced changes in s-IgA were due to changes in health practice can not be ruled out.

The literature on the effects of psychobehavioral intervention on s-IgA is promising but preliminary. These studies tested various intervention techniques and short term increases in s-IgA were observed. It is not clear how long these changes persist and it is not yet known whether these interventions will buffer the effects of stress on s-IgA as none of the studies exposed subjects to stress after they had undergone the intervention. The clinical significance of these changes is also not known. The only study that assessed number of symptoms (Rider et al., 1990) found that subjects who were trained in relaxation had higher levels of s-IgA and reported fewer symptoms during the study, however, the particular symptoms affected were not immune related (breathing difficulty, jaw clenching and rapid heartbeat).

It is not clear through which mechanism these interventions affected s-IgA. These interventions presumably reduce subjective distress and physiological arousal. Only two studies included neuroendocrine assessments (Green & Green, 1987; Jasnoski & Kugler, 1987) and both studies reported that there was no change in these measures following the intervention. Surprisingly, of the three studies (Green et al., 1988; Rider et al., 1990; Groer et al., 1994) that assessed psychological distress only one study (Rider et al., 1990) observed a decrease in psychological distress after the intervention. Systematic investigation of the mechanism underlying the effects of psychosocial interventions on s-IgA are needed, as those studies will provide information about both the clinical significance of psychosocial interventions and the possible primary and secondary mechanisms underlying the relation between stress and s-IgA.

It is clear that there has been a considerable effort to understand how the psychosocial environment affects s-IgA. While the majority of studies support an association, several issues about this literature remain problematic and should be the object of future research. Results are not consistent among studies using s-IgA concentration and secretion rates as outcomes. The resolution of these issues may lie in the proper measurements of salivary flow. Questions have been raised about the meaning of total s-IgA assessments, and empirical work is needed to convincingly show health consequences of total and/or specific measures of s-IgA. Psychologic and physiological pathways translating environmental events into changes in s-IgA also need to be systematically investigated.

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